Why did I get Parkinson's disease?

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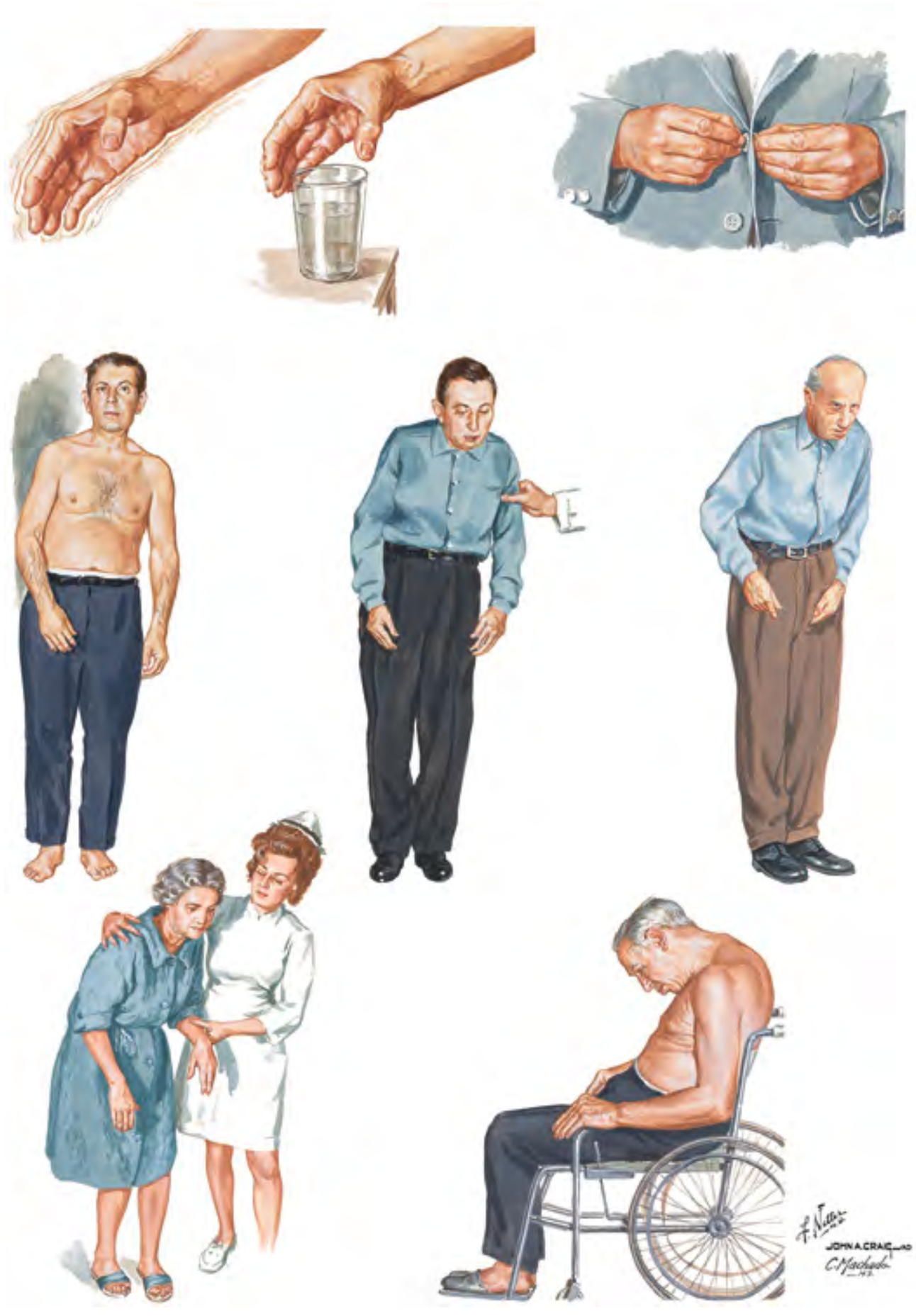
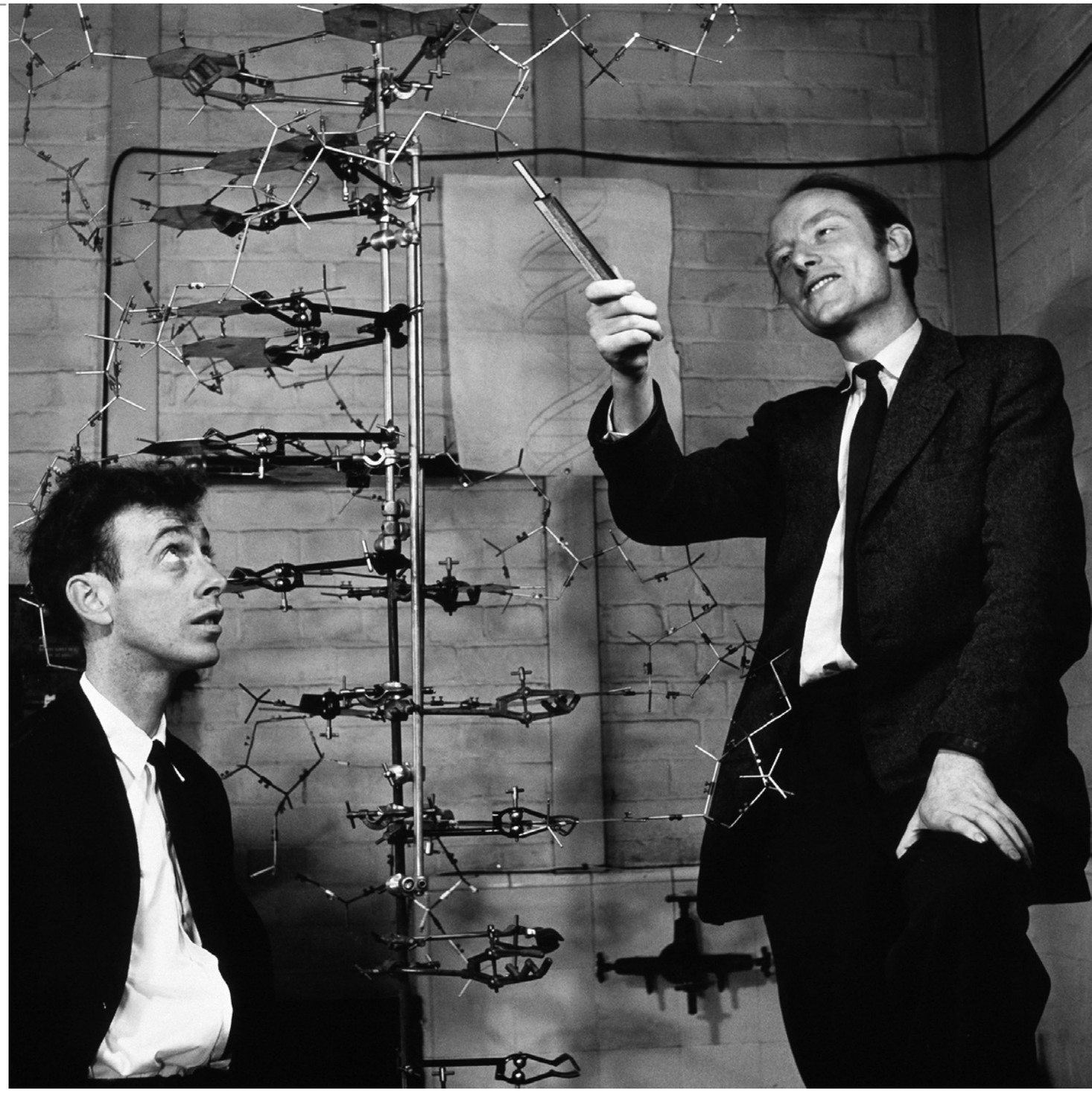
Not alone…

- 2% risk of Parkinson's (PD)
- About 1 million Americans have it
- About 2 million will have it by 2030
- $25 billion a year in the US alone



Nature

- Age and sex
- Familial factors
- Genetic factors



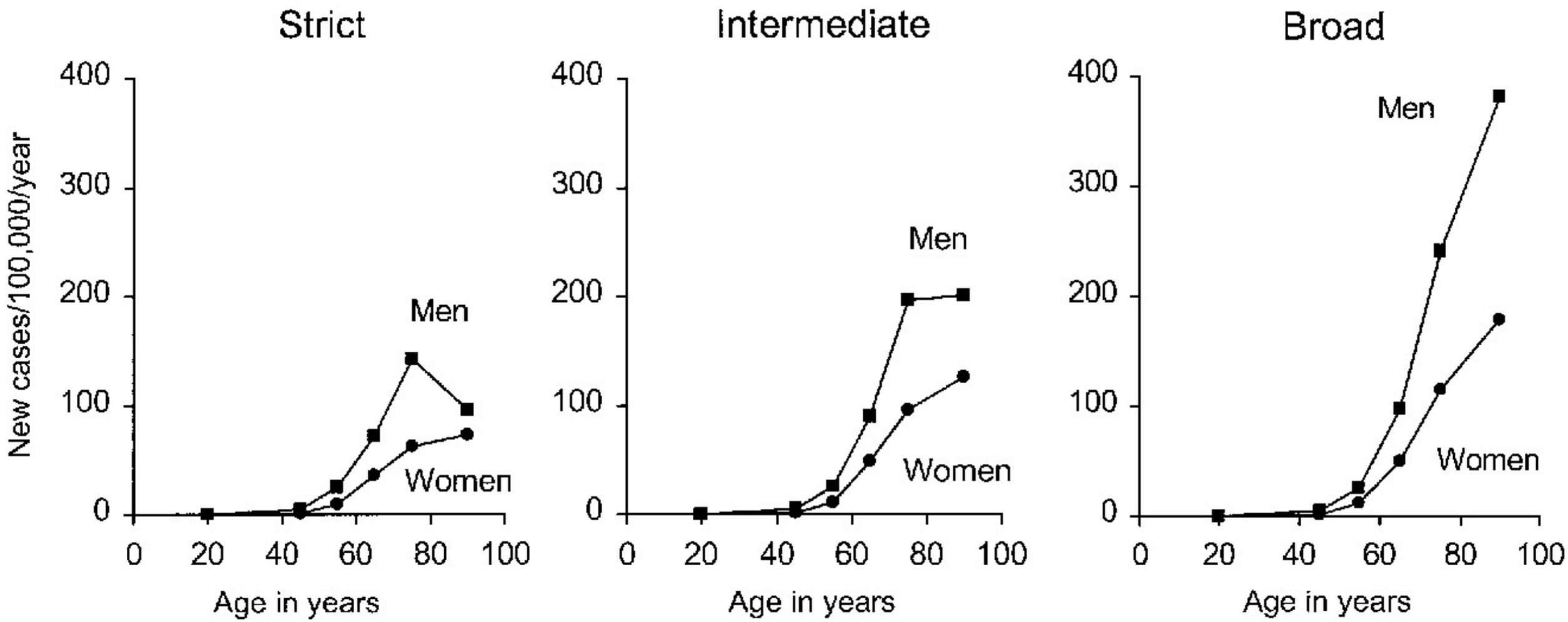
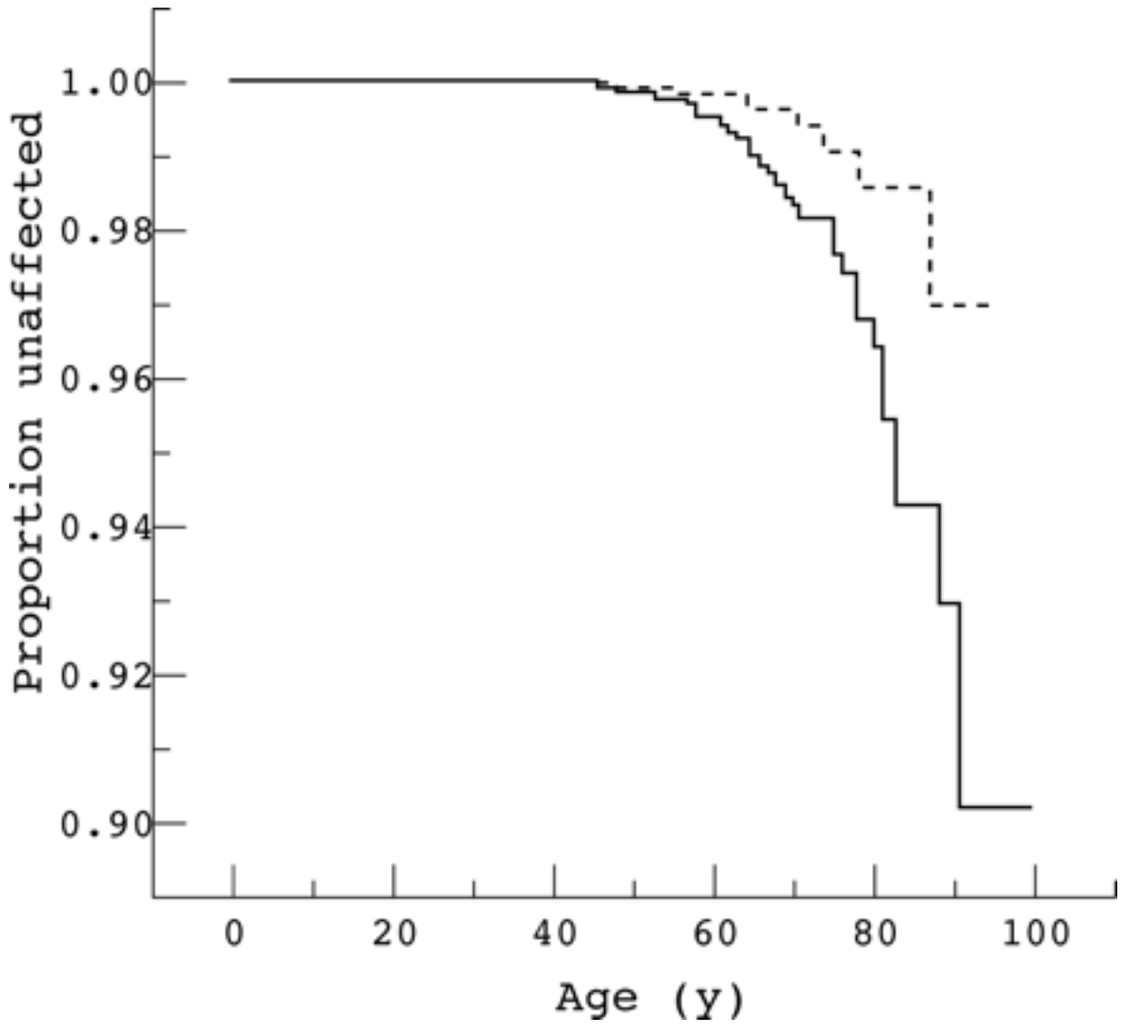


FIG. 1. Influence of three sets of diagnostic criteria (strict, intermediate, broad) on age- and sex-specific incidence rates (new cases per 100,000 person-years) of Parkinson's disease, Olmsted County, MN, 1976–1990.

Age | men more than women

Familial factors

- First degree relatives of PD cases have a 2-3x increased risk of PD
- First degree relatives also have an increased risk of tremor, dementia, anxiety, depression
- These risks are greater for the first degree relatives of younger PD cases
- Segregation analyses suggest genetic causes



Causal gene variants: rare but big effects

SNCA

PRKN

UCHL1

DJ1

PINK1

LRRK2

ATP13A2

DNAJC6

DNAJC13

VPS35

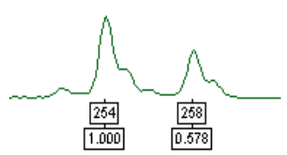
EIF4G1

PLA2G6

FBX07

OTHERS


254
1.000
258
0.978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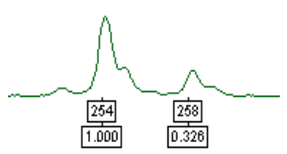
0.578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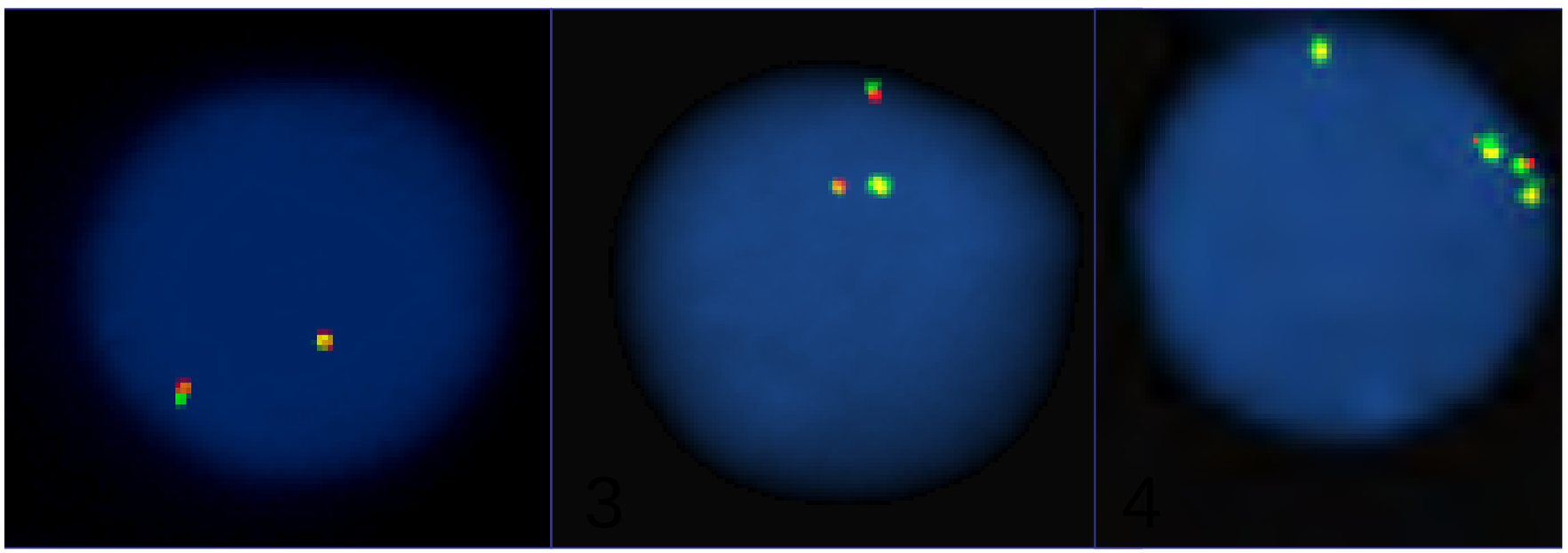
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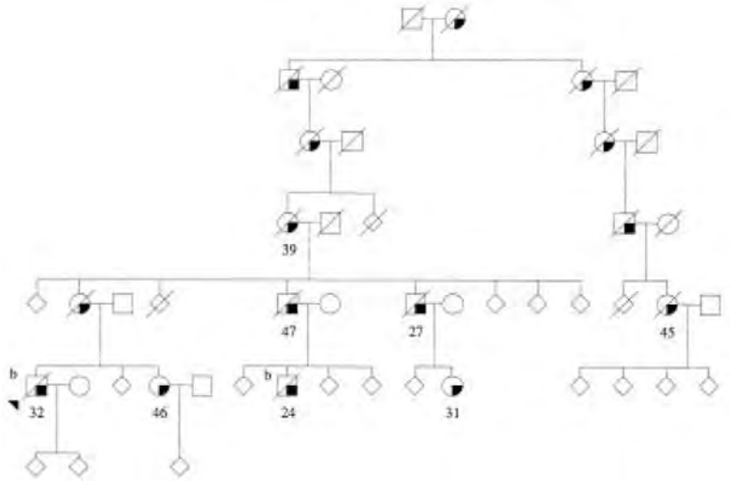
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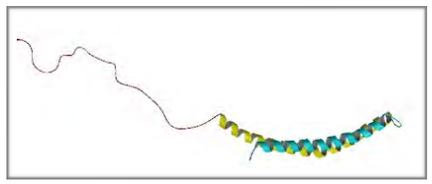
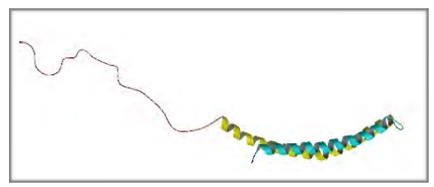
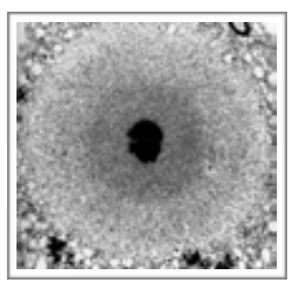
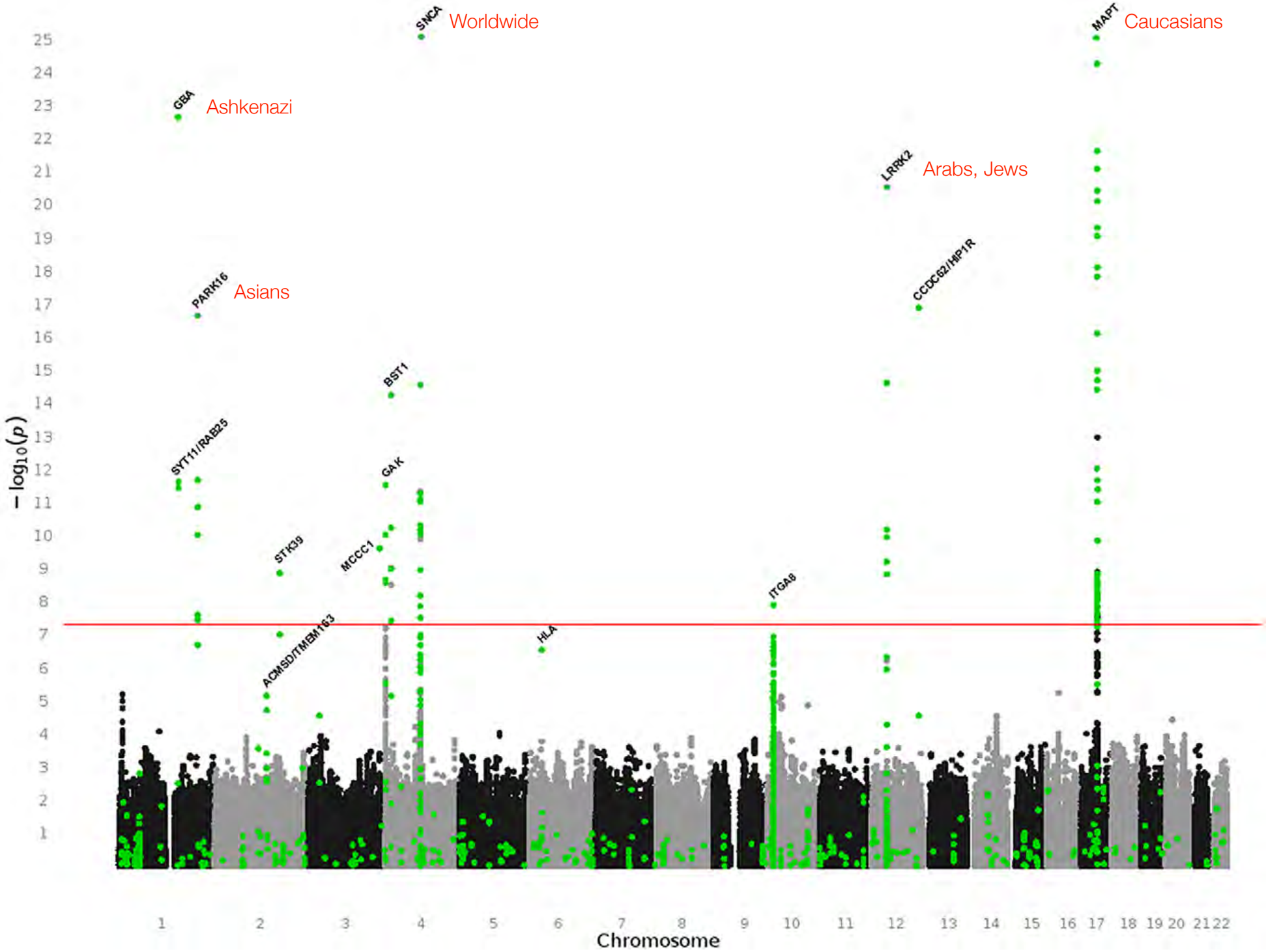






α-synuclein

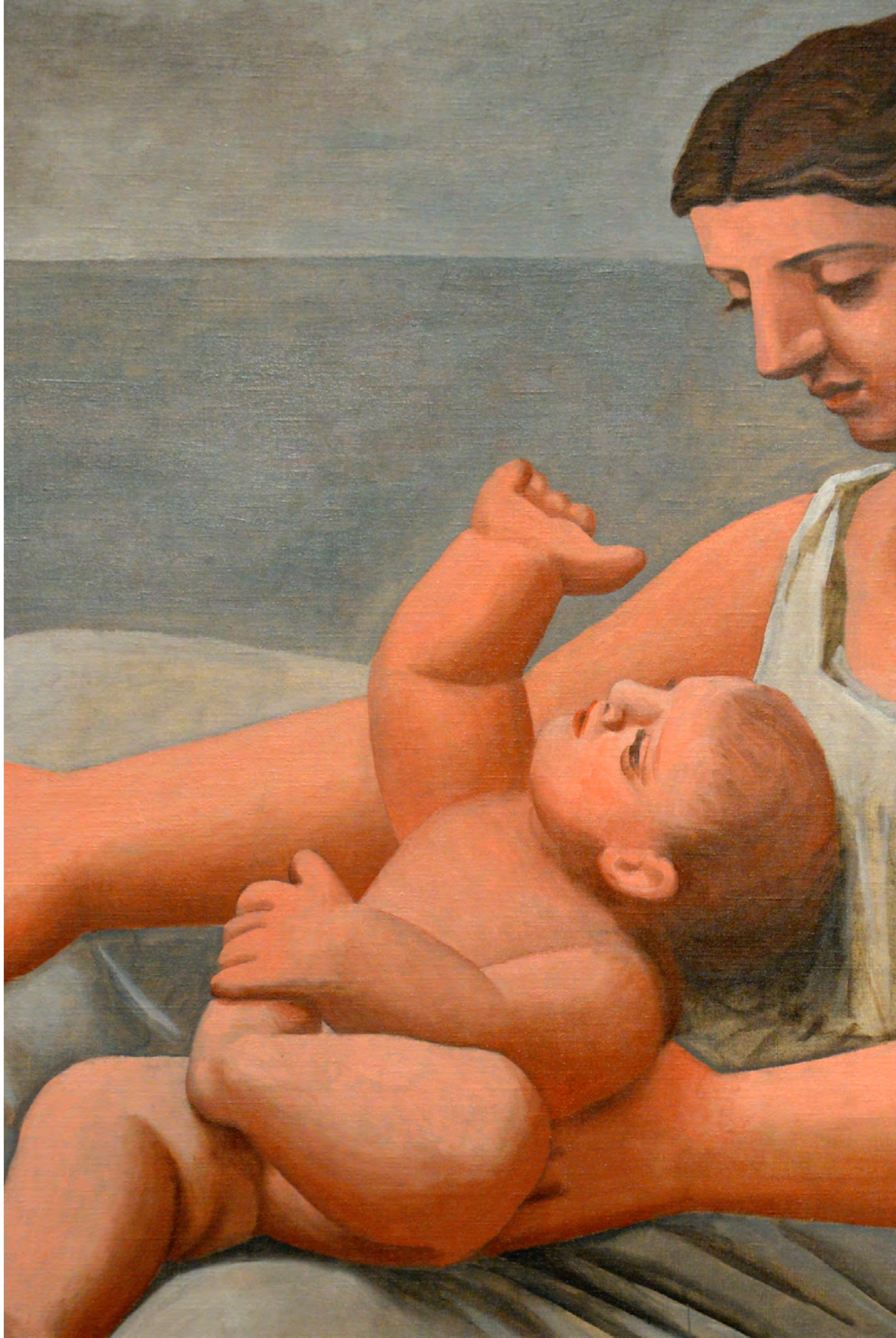


Susceptibility variants

common but small effects (1.2 x)

Nurture

- Pesticides
- Head trauma
- Habits
- Occupation
- Childbearing
- Hormonal



Pesticides

- Pesticides exposure increases the risk of PD (2x)
- The risk is in men only
- Occupational and hobby exposures both carry risk
- The risk is greater for herbicides and insecticides than fungicides

Head trauma

- Head trauma increases risk (4x)
- Head trauma with hospitalization increases risk (8x)
- Head trauma with loss of consciousness increases risk (11x)
- Effect primarily in men

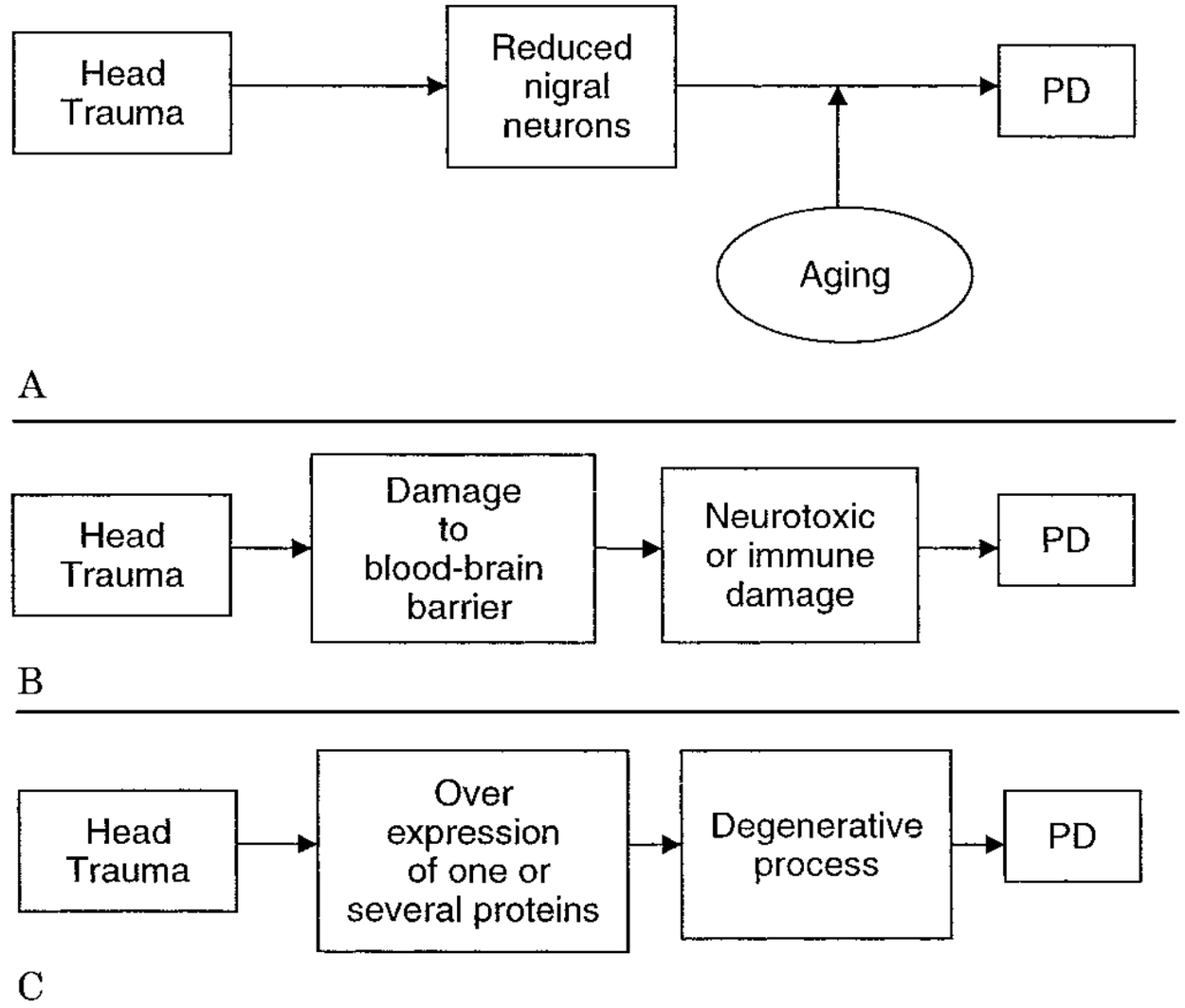
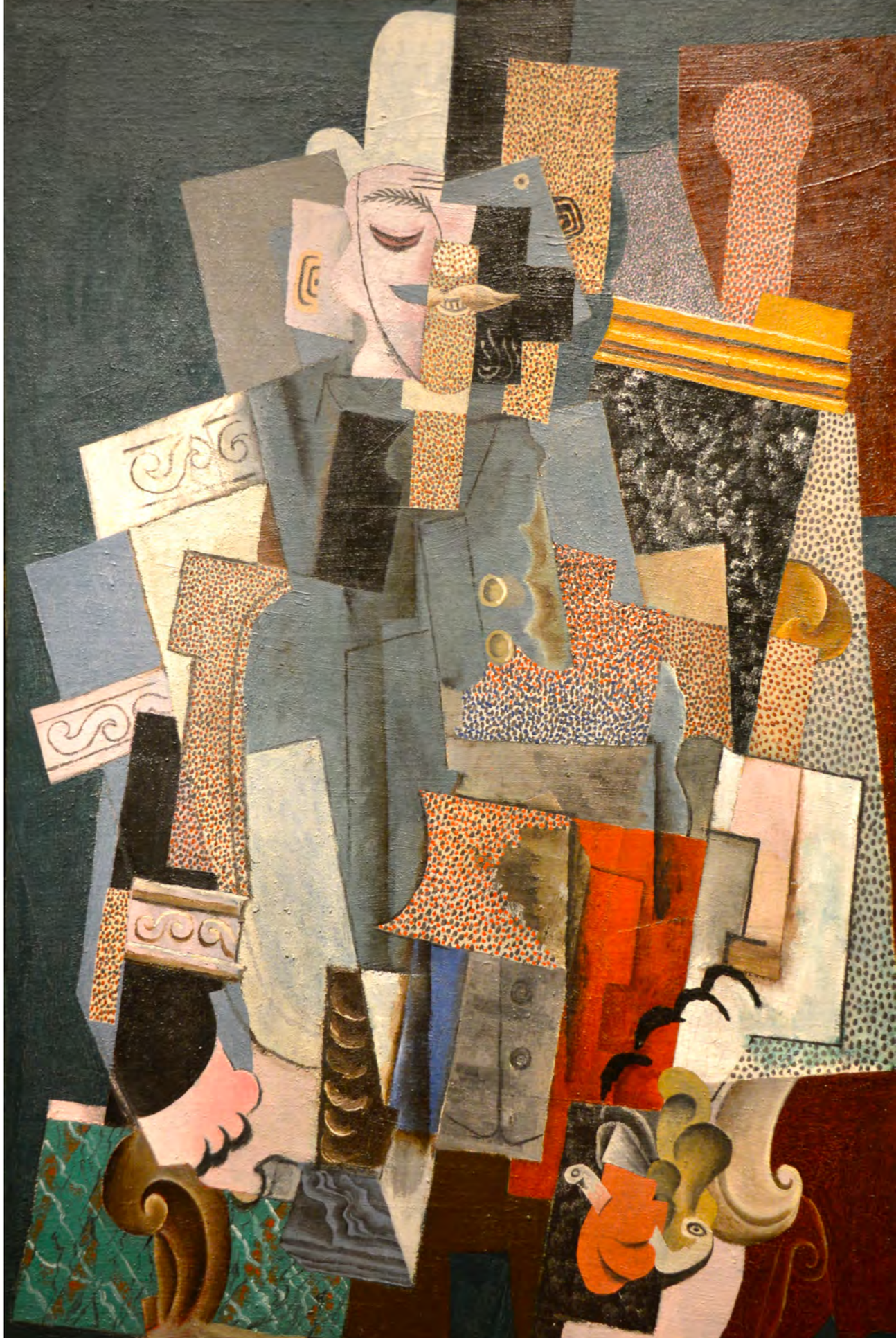


Figure. Three hypotheses of the possible mechanisms linking head trauma to PD. (A) Head trauma contributes to the neuronal loss in the substantia nigra occurring normally with aging. (B) Head trauma damages the blood–brain barrier, allowing an exogenous toxin or the immune system to damage the brain. (C) Head trauma causes the overexpression of one or several proteins that interfere with protein processing, thus causing protein deposition and cell death.

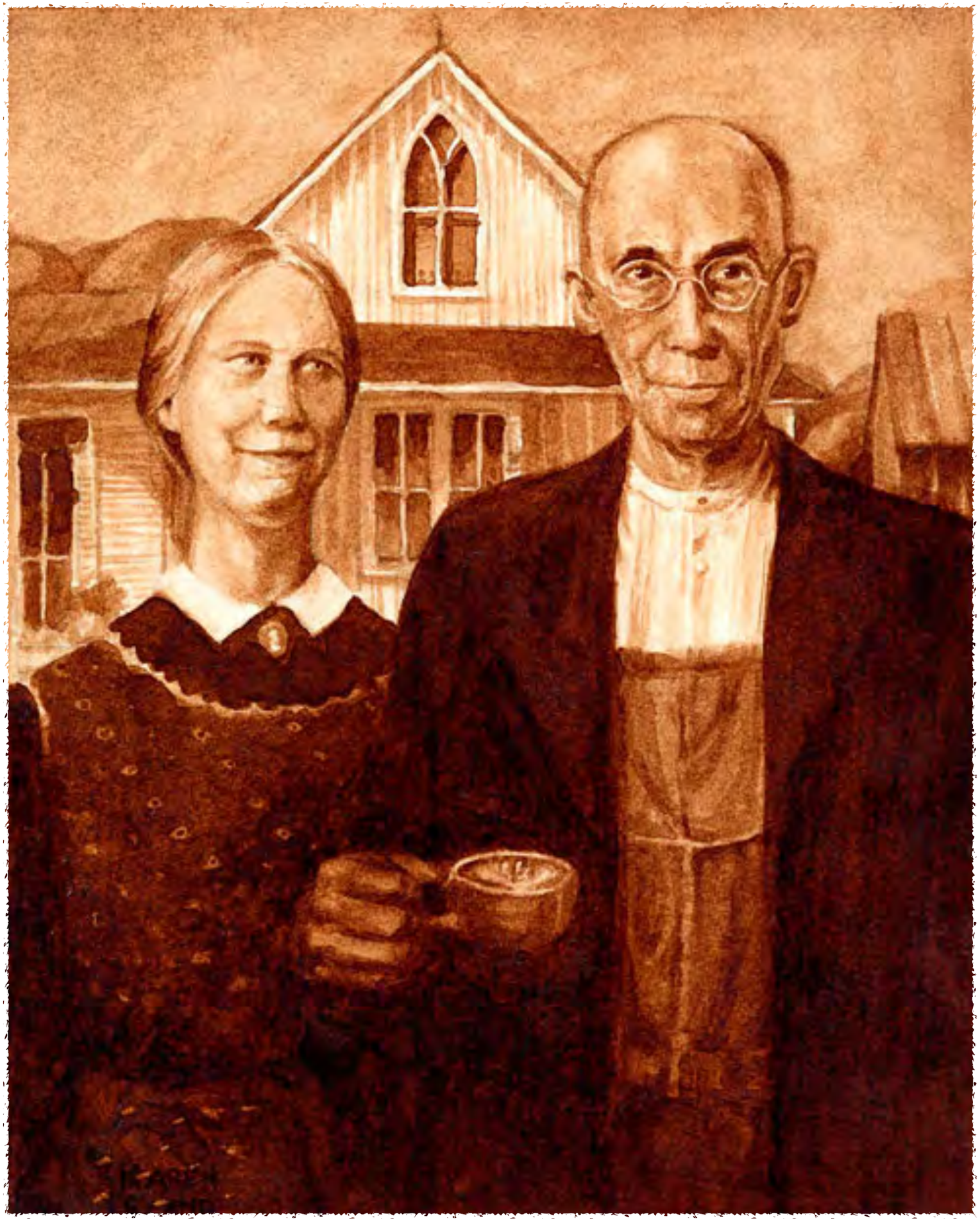
Smoking (habits)

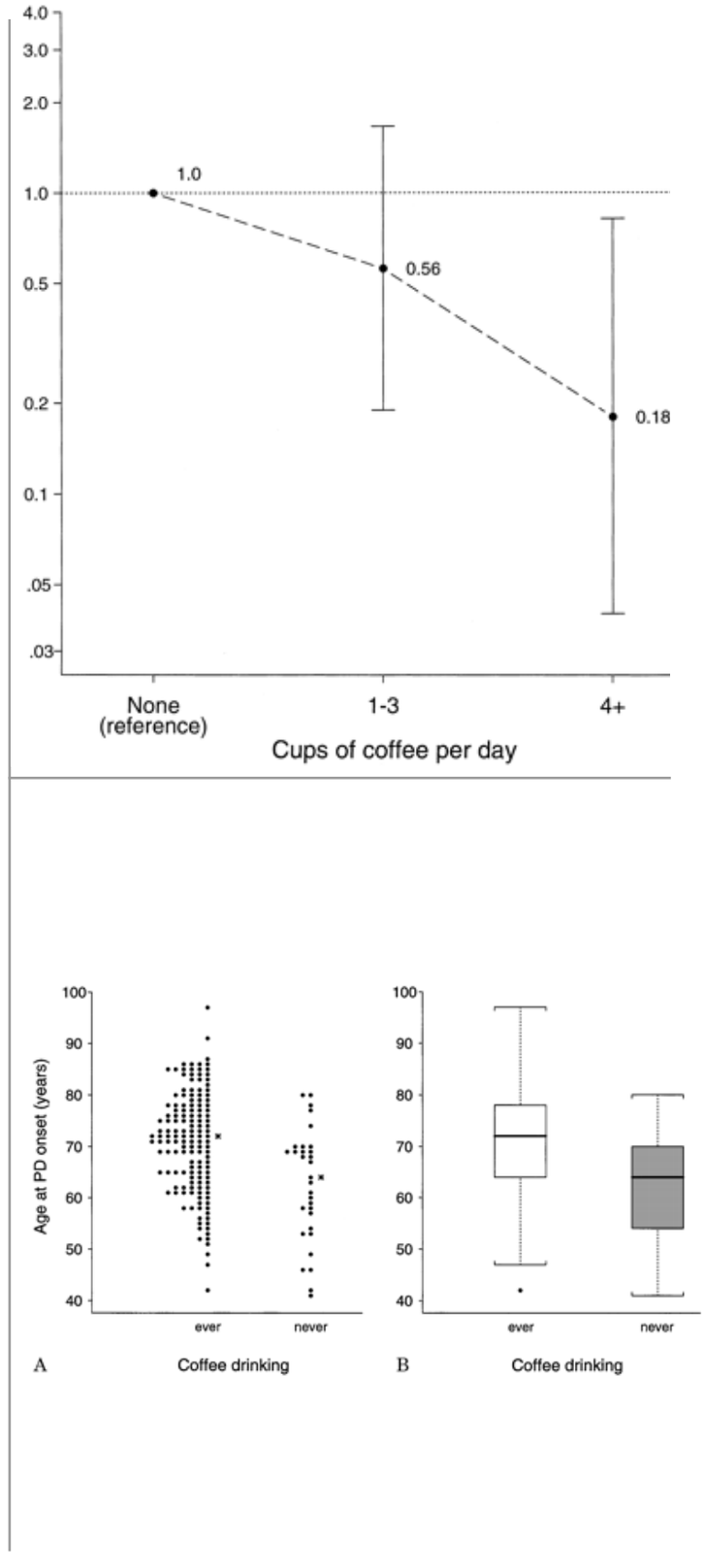
- Smokers have a 50% lower risk of PD
- Non-smokers have double the risk of PD
- The more you smoke (pack-years) the lower the risk of PD
- Extreme use (chewing, snuff) carries the lowest risk of PD



Coffee (habits)

- Coffee drinkers have a 50% lower risk of PD
- Never drinkers have double the risk
- More cups, lower risk
- The reduced risk is primarily in men





Dose effect, age at onset

Alcohol (habits)

- Alcohol drinking does not reduce the risk of PD
- However, alcoholics have a 50% lower risk
- **Pattern:** extreme use of smoking, coffee, and alcohol are all associated with a reduced risk of PD

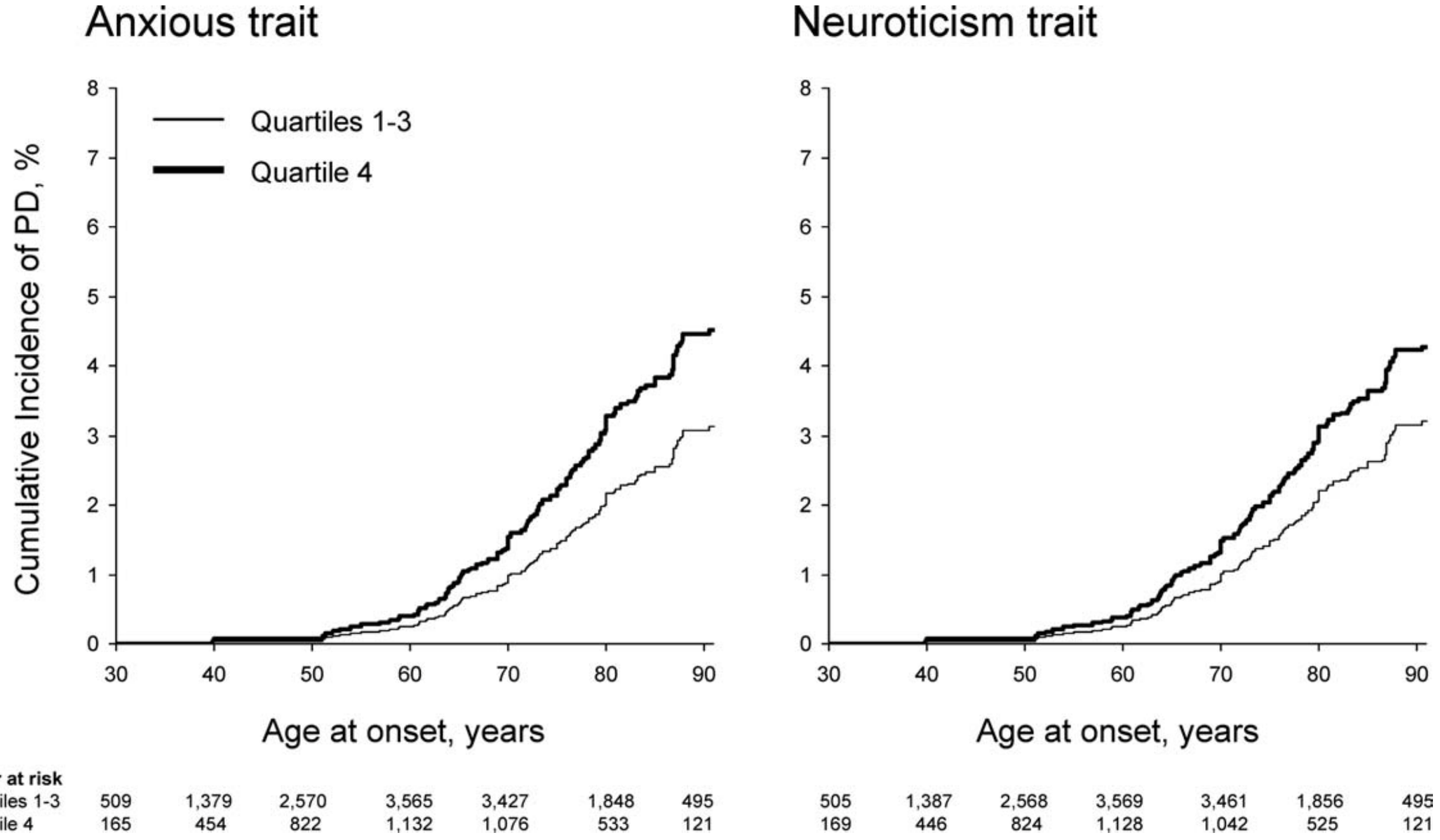


FIG. 2. Cumulative incidence of PD in men and women combined: comparison of subjects in the top quartile with subjects in quartiles 1−3 of the anxious personality trait (HR = 1.63; 95% CI = 1.16−2.27; $P = 0.004$) and of the composite neuroticism score (HR = 1.54; 95% CI = 1.10−2.16; $P = 0.01$). The graphic display accounts for death as a competing risk.[29]

Confounding?

reduced dopamine, reduced pleasure seeking
reduced dopamine, reduced reward
reduced dopamine, anxious and nervous state
reduce dopamine, Parkinsonism

TABLE 1

Pearson's correlation coefficients for the relation between baseline food intakes and factors representing dietary patterns in the Health Professionals Follow-Up Study (1986) and the Nurses' Health Study (1984)[1]

	Men		Women	
Food	**Factor 1 (prudent)**	**Factor 2 (Western)**	**Factor 1 (prudent)**	**Factor 2 (Western)**
Other vegetables	0.75	—	0.67	—
Leafy vegetables	0.64	—	0.63	—
Yellow vegetables	0.63	—	0.60	—
Cruciferous vegetables	0.63	—	0.61	—
Legumes	0.61	—	0.55	—
Fruit	0.58	—	0.60	—
Tomatoes	0.56	—	0.45	—
Fish	0.51	—	0.50	—
Garlic	0.42	—	0.34	—
Poultry	0.36	—	0.43	—
Whole grains	0.35	—	0.41	—
Red meat	—	0.62	—	0.56
Processed meats	—	0.58	—	0.56
Refined grains	—	0.49	—	0.58
Desserts and sweets	—	0.47	—	0.44
French fries	—	0.46	—	0.47
High-fat dairy products	—	0.44	—	0.36
Eggs	—	0.38	—	—
High-sugar drinks	—	0.39	—	0.34
Snacks	—	0.37	—	—
Condiments	—	0.35	—	0.43
Margarine	—	0.35	—	0.33
Potatoes	—	0.34	—	0.42
Low-fat dairy	—	—	0.35	—
Olive oil	—	—	0.33	
Mayonnaise	—	—	—	0.31
Pizza	—	—	—	0.35

[1] Correlation coefficients <0.3 were omitted for simplicity.

Diet (habits) | "prudent diet" reduces risk by 20%

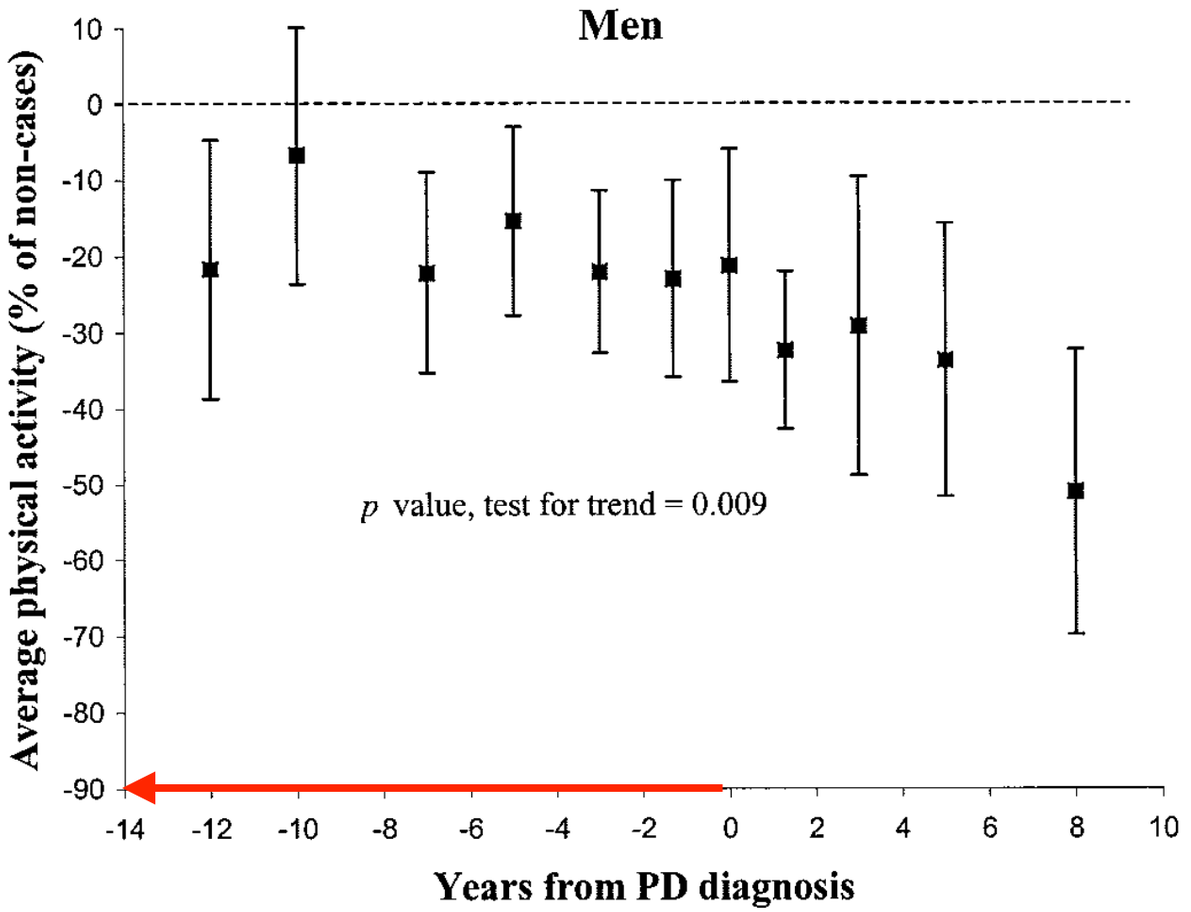


Figure 1. Average physical activity of Parkinson disease (PD) cases as percentage of noncases at different time points before and after the diagnosis in men, adjusting for age, age squared, and smoking status for each time period. The sample size at each time point ranges from 48 to 228. The reference line represents the average values of individuals without PD.

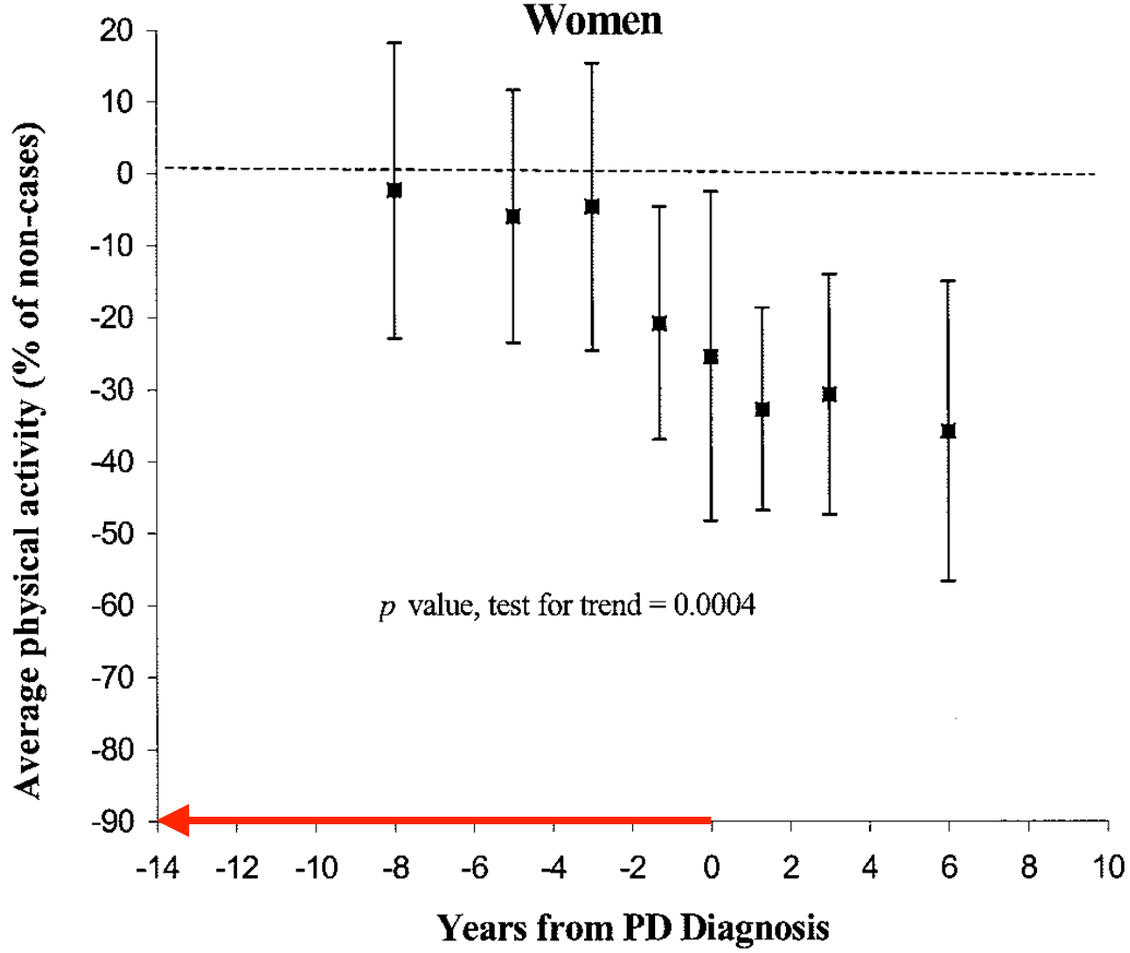


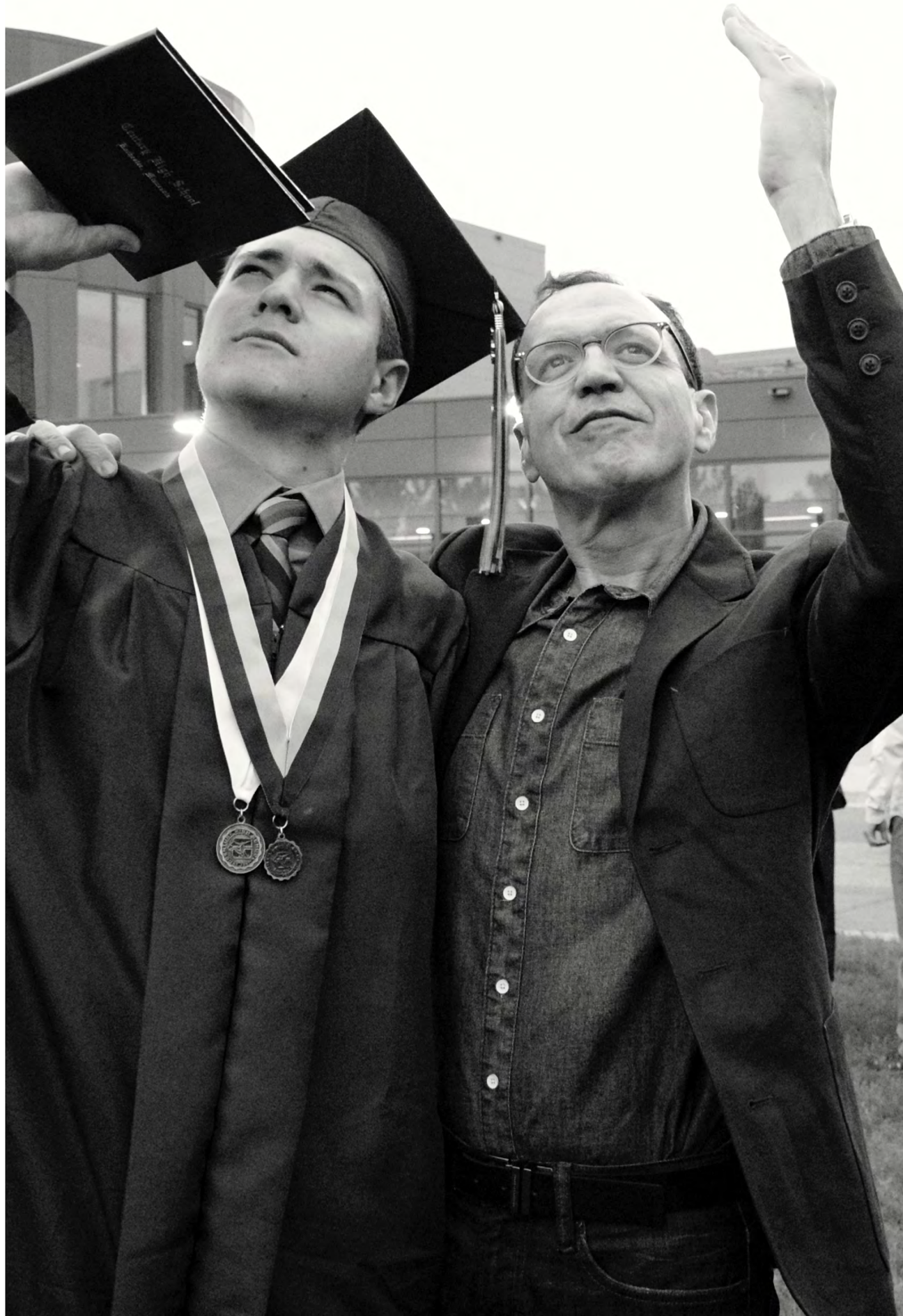
Figure 2. Average physical activity of Parkinson disease (PD) cases as percentage of noncases at different time points before and after the diagnosis in women, adjusting for age, age squared, and smoking status for each time period. The sample size at each time point ranges from 57 to 115. The reference line represents the average values of individuals without PD.

Exercise (habits)

Physical inactivity increases risk by 30% (men)

Occupation

- Higher education is associated with a 2-3x increased risk of PD
- Physicians carry an increased risk
- Physical jobs carry a reduced risk
- Ascertainment bias?
- Reverse causation?

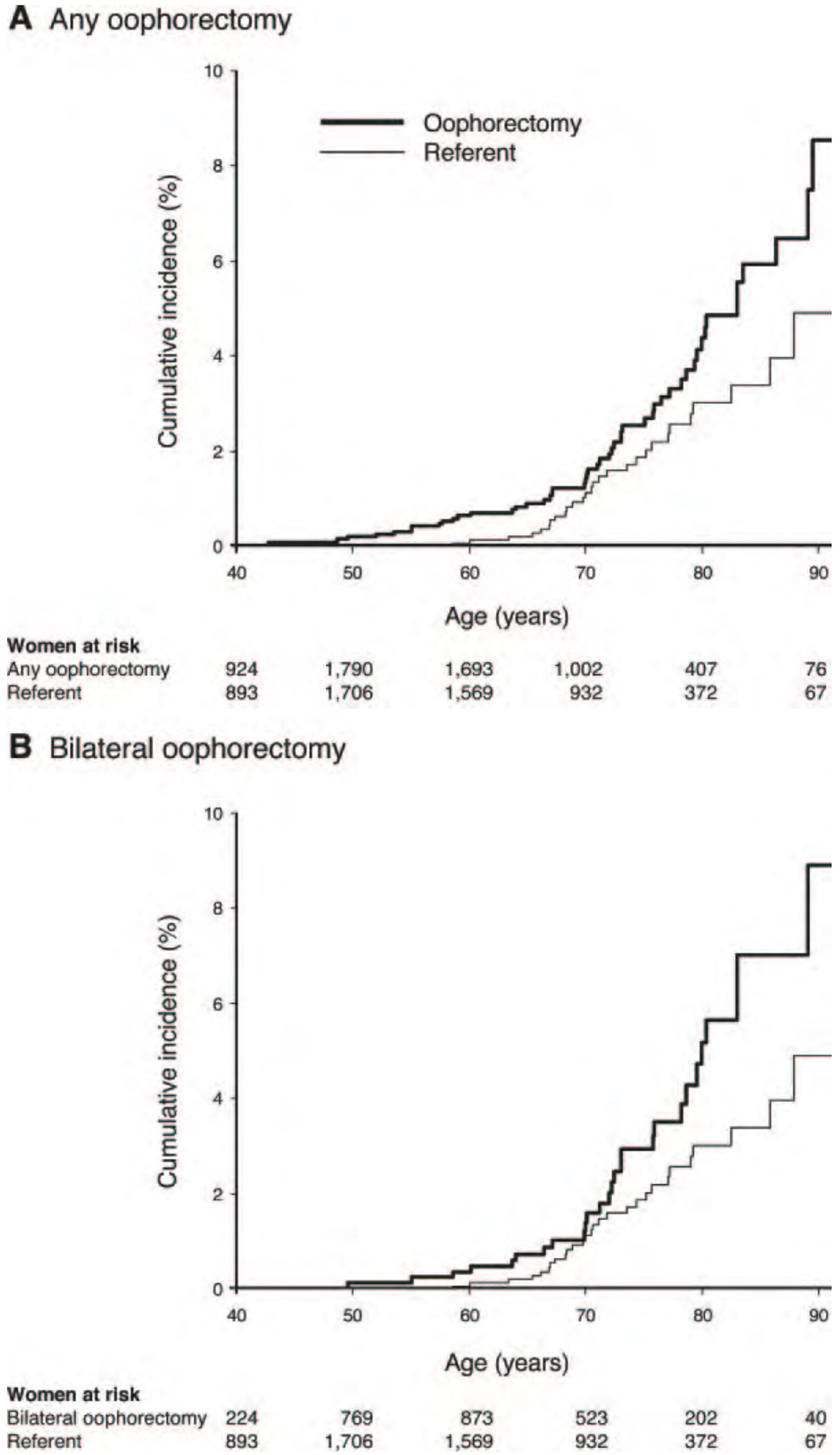


Childbearing

- Men who have children are at greater risk of PD
- More children, greater risk
- Reverse causation?

Hormonal

- Women who undergo ovariectomy are at increased risk of PD (2x)
- The risk is greater for bilateral ovariectomies (dose effect)
- The risk is greater for women who had surgery at younger ages
- Is estrogen neuroprotective?
- Does this explain why many risk factors for PD are not in women?



Unifying hypothesis

- Gene x Environment interactions

- We are born with factors that make us more likely (e.g., genes) or less likely (e.g., female sex) to get PD

- We are exposed to factors that make us more likely (e.g., head trauma) or less likely (e.g., exercise, diet) to get PD

- As we age the effects of genes and the environment add up, or multiply, causing brain cells to degenerate

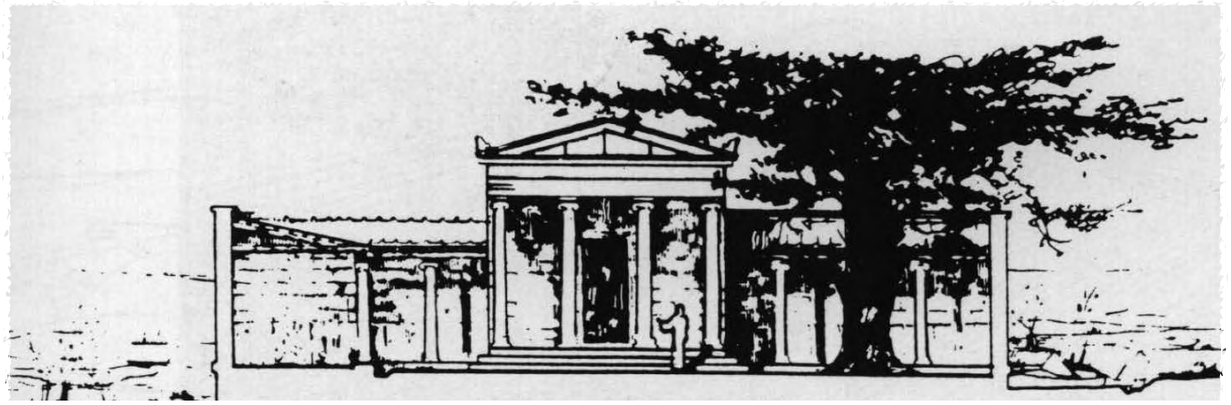
- That is why we get PD

What to do now?

- Learn more about it
- Exercise
- Diet
- Get the best care
- Engage in research

Engage in research

- The DodoNA Project: DNA predictions to improve neurological health
- The Genetic Epidemiology of Parkinson's Disease Consortium
- Imaging biomarkers of delayed sequelae in mild traumatic brain injury
- Intrinsic re-modeling of the fovea in PD
- Automated multiparametric quantitative MRI assessments in PD



http://www.northshore.org/neurological-institute/research-innovation/

Team

First row: Debi Crystal, Roberta Frigerio, Monika Szela, Beth Rose, Ashvini Premkumar, Jim Maraganore, Faith Langtiw, Dora Kafkas

Second row: Lindsay Lucas-Kamm, Nanci Maroney, Katerina Markopoulou, Alona Ramati, Bernadette Schoneburg, Julie Anderson, Nazia Kazmi, Mia Boelen

Third row: Diane Mattson, Jim Castle, Chad Yucus, Tamara Meyer, Karen Henrickson, Athie Roniotis, Laura Ames

Not shown: Rachel Kerman, Shaun O’Leary, Violet Potocki